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Short Report

An unaffected individual from a breast/ovarian cancer family with germline mutations in both *BRCA1* and *BRCA2*

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Currently many centers offer testing for three specific mutations, 185delAG, 5382insC, and 6174delT, in the *BRCA1* and *BRCA2* genes to Ashkenazi Jewish individuals at high risk for breast and ovarian cancer. We recently tested members of a family with multiple cases of breast and ovarian cancer (Family R014). The proband in this family tested positive for the 185delAG mutation. The unaffected sister of the proband tested positive for both the 185delAG and the 6174delT mutations. Further testing and review of the family history suggest that both mutations may have come from a maternal grandfather and passed down for two generations. Counseling of the unaffected double heterozygote individual in this family is complicated by lack of information on the risk of breast, ovarian, and other cancers in such individuals. A better understanding of these risks will depend on the identification and study of more individuals carrying mutations in both the *BRCA1* and *BRCA2* genes. Our study emphasizes the importance of testing Ashkenazi Jewish individuals from high-risk breast and ovarian cancer families for all three common *BRCA1* and *BRCA2* mutations identified in this ethnic group.

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To date, three common *BRCA1* and *BRCA2* mutations have been reported in breast and ovarian cancer families from Ashkenazi Jewish descent (1–3). The frequency of the *BRCA1* 185delAG mutation in the overall Jewish population has been estimated at 1.05% (1, 2). The second *BRCA1* mutation, 5382insC, is estimated to exist at a frequency of 0.1% in the Jewish population (1, 2). The third mutation, 6174delT, is in the *BRCA2* gene and is thought to exist at a frequency of 1.4% in the Jewish population (2, 3).

We report a family with an unaffected double heterozygote female who inherited a *BRCA1* and a *BRCA2* mutation from one parent.

Case report

Family R014 was ascertained through individual 45 as part of a research project on Ashkenazi Jewish women with ovarian cancer. The proband had unilateral breast cancer diagnosed at age 30 years. She had re-occurrence of cancer in the same breast at age 38 years, four months *post partum*. She then developed ovarian cancer at age 39 years. She died at age 41 from ovarian cancer.

The family (Fig. 1) is remarkable for ovarian cancer in the mother of the proband (individual 38) diagnosed at age 36. There is a family history of early-onset breast cancer in the proband's ma-

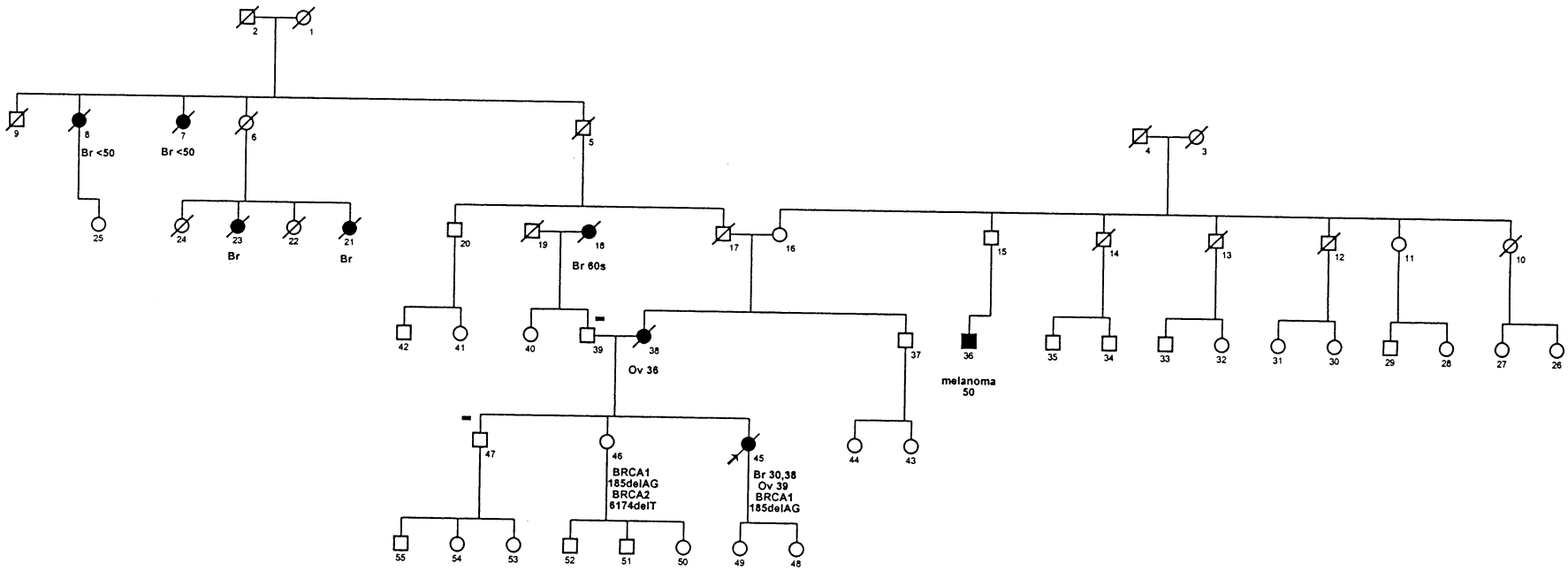

Fig. 1. Pedigree of Family R014. Black circles indicate women affected with cancer. Black squares indicate men affected with cancer. Diagonal slash indicates deceased. Numbers immediately below symbols are individual identification numbers. Br: breast cancer, Ov: ovarian cancer. The numbers following abbreviations indicate the age of diagnosis. The mutation found is indicated below the symbols. A minus sign indicates the absence of the *BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT mutations.

ternal great grandfather's family. The proband had two maternal great great aunts with early-onset breast cancer and two distant cousins with early-onset breast cancer. There is no family history of breast or ovarian cancer in the proband's maternal grandmother's family.

The proband was tested for the three common mutations in the Ashkenazi Jewish population, the 185delAG, 5382insC, and 6174delT mutations. Mutation analysis was performed by amplifying exons 2 and 20 in the *BRCA1* gene and exon 11 in the *BRCA2* gene using standard PCR amplification protocols. SSCP analysis of exon 20 and heteroduplex analysis of exon 2 of the *BRCA1* gene and protein truncation test (PTT) of exon 11 of the *BRCA2* gene were performed to identify aberrant DNA. The aberrant bands were then sequenced using a standard protocol as outlined in Amersham sequencing kits, US70170 and US79750. All mutations were confirmed.

The proband tested positive for the 185delAG mutation in the *BRCA1* gene. Genetic testing was offered to other family members. Three other first-degree relatives, individuals 39, 47, and 46, were tested for the three mutations.

Proband's brother and father tested negative for the three mutations. Proband's sister, individual 46, tested positive for both the 185delAG and the 6174delT mutations. Individual 46, who was 36 years old, had never been diagnosed with cancer and had not undergone any prophylactic surgery.

Paternity was confirmed by using 5 polymorphic markers D1S249, D2S293, D2S172, D6S434, and D8S537 and testing individuals 39 and 46.

Discussion

Individual 46 is the first reported case of an unaffected woman inheriting mutations in both the *BRCA1* and *BRCA2* genes from one parent. This individual is the second reported case of an unaffected *BRCA1*/*BRCA2* double heterozygote. Proband's father (individual 39) is negative for all three mutations. Therefore, proband's mother (individual 38) is assumed to have been a 185delAG/6174delT carrier. Individual 38 is deceased and tumor blocks are not available for testing.

Individual 16, who is the mother of individual 38, is 88 years old and has never had cancer or prophylactic surgery. According to the current estimates of penetrance of the *BRCA1* and *BRCA2* mutations, individual 16 has about 8% probability of carrying either the 185delAG or the 6174delT mutations without developing breast or ovarian cancer by age 88 years (4). The observation that many female relatives of individual 16 lived to an old age and never developed breast or ovarian cancer supports the assumption that there is no mutation segregating in that side of the family. Therefore, there is a much higher likelihood that individual 38 inherited both mutations from her double heterozygote father, individual 17. This could then be a case of a two-generation inheritance of two mutations in the *BRCA1* and *BRCA2* genes from one parent to one child.

The high population frequency of the 185delAG and the 6174delT mutations in the Jewish population makes it possible for a Jewish individual to be a double heterozygote; this probability is 0.014%.

Friedman et al. (1998) reported a breast cancer patient of Ashkenazi Jewish origin with both the 185delAG and the 6174delT mutations. This individual may have inherited both mutations from her mother who had ovarian cancer (5). This group also reported three other Ashkenazi Jewish women, two of whom were affected with either breast or ovarian cancer, who were 185delAG/6174delT mutation carriers (5). The third woman in their study was a 50-year-old asymptomatic Ashkenazi Jewish woman with a maternal family history of breast and ovarian cancer and a paternal history of prostate cancer. None of the parents in this case were available for testing (5).

Another group reported an Ashkenazi Jewish individual with breast cancer with both the 185delAG and the 6174delT mutations (6). We recently reported a family segregating all three common Ashkenazi Jewish mutations (7). No double or compound heterozygote individuals were found in that family. There is also a report of a non-Jewish breast cancer patient with germline mutations in the *BRCA1* and *BRCA2* genes (8).

Friedman et al. reported that 2 of their double heterozygote patients had reproductive problems. Individual 46 in our family did not indicate any problems with fertility or premature menopause, but two of her seven pregnancies ended in miscarriages. We do not have a detailed reproductive history on individual 38.

The penetrance of the *BRCA1* and *BRCA2* mutations has been reported to be highly variable for breast and ovarian cancers and may differ based on the position of the mutation in the gene (9, 10). The current estimate of breast cancer is between 76 and 87% life-time risk (by age 75) for mutations in the *BRCA1* gene and slightly lower for *BRCA2* mutations (4, 11–13). The estimate of the risk of ovarian cancer is between 32 and 84% for *BRCA1* mutations and 20 and 40% for *BRCA2* mutations (11–13). These estimates, however, were obtained by studying families with a high incidence of breast and ovarian cancers. Recent studies suggest that

the penetrance of the 185delAG and 6174delT mutations for breast and ovarian cancers in an unselected population may be less than previously reported (14).

Due to the small number of 185delAG and 6174delT double heterozygotes identified to date, there are currently no data available on the risk of breast and ovarian cancers in these individuals. There has been a suggestion that the phenotypic effects of double heterozygosity for *BRCA1* and *BRCA2* germline mutations may not be cumulative (5). In our family, individual 46 with both the 185delAG and 6174delT mutations remained unaffected to age 36 years, while her sister with the 185delAG mutation was diagnosed with breast cancer at age 30 years. Individual 38, who is inferred to have carried both of these mutations, also did not develop breast or ovarian cancer until age 36 years.

There is also no information available on the risk of other cancers in individuals who carry mutations in both *BRCA1* and *BRCA2* genes. The implication of carrying both the 185delAG and the 6174delT mutations for a male is also unclear. In our family, individual 17, who is inferred to have carried both of these mutations, lived to age 70 without developing cancer. He died in his 70's of an unknown cause.

Individual 46 in our family was counseled as having at least the same risk of breast and ovarian cancers as a carrier of the 185delAG mutation, such as her sister. She subsequently decided to have prophylactic oophorectomy and bilateral mastectomy.

Identifying individuals with mutations in both the *BRCA1* and *BRCA2* genes has both clinical and scientific relevance. Accurate genetic counseling and medical management of *BRCA1*/*BRCA2* double heterozygotes will depend on studying the reproductive, medical, and family history of such individuals. These studies also enhance understanding of the mechanism of action of these genes and their interactions.

Our finding further emphasizes that all Ashkenazi Jewish individuals at high risk for breast and ovarian cancers be tested for all three common Ashkenazi Jewish mutations regardless of the mutation previously identified in the family.

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